Reconsidering brain tissue changes as a mechanistic focus for early intervention in psychiatry

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Following a first episode of psychiatric symptoms, patients have a high risk of subsequent episodes of similar or variable nature. These subsequent recurrences characterize relapses[1,2] as well as comorbidity[3] depending on the nature of the first episode. After the first episode of psychosis, more than 50% experience a relapse within 3 years, with each relapse further increasing the risk of subsequent episodes over time.[4] Such recurrences are assumed to indicate a temporal progression in the underlying illness process.[5] The pathobiological mechanisms for these recurrences are hitherto unknown. Nevertheless, interrupting these unknown mechanistic processes has been the focus of long-term secondary prevention strategies after the first episode of serious mental illnesses such as schizophrenia,[6] depression[7] and bipolar disorder.[8]

Among various psychiatric disorders, secondary prevention (i.e., early intervention) strategies are best established for psychotic disorders. The rationale for the adoption of these strategies is irrefutable; early intervention in psychosis shortens the duration of personal suffering,[9] minimizes the psychosocial toxicity of untreated psychosis and promotes occupational achievement.[10,11] While the utilitarian argument is well established, the mechanistic rationale for early intervention in psychosis is built on targeting the underlying pathophysiology to arrest illness progression.[12] Structural brain abnormalities have been one of the most widely investigated features in this regard. Untreated illness is considered detrimental to brain structure, and early intervention is said to improve outcomes by arresting longitudinal reduction in grey matter tissue, termed "neuroprogression."[13] The notion of disease modification by thwarting neuroprogression has also become the key theme for advocating early intervention in other severe mental illnesses such as bipolar disorder,[14] depression[15] and obsessive–compulsive disorder.[16] Despite the enthusiastic adoption of the idea of neuroprogression in the field of early intervention, several critical questions regarding this concept remain unanswered. In this editorial, we present an overview of neuroprogression in psychosis and argue for an alternative conceptual model for the neuroscience of early intervention. What follows is not a critique on the need for early intervention, which in our opinion is indisputable for every psychiatric disorder.[17] Here we evaluate the mechanistic premise that is repeatedly invoked when discussing early intervention in psychiatry. While demonstrable brain changes are not required for early interventions to be effective, a fresh neuroscientific framework can accelerate treatment discovery and be impactful to deliver the next generation of transdiagnostic early intervention.[18]

Is there a progressive loss of brain tissue in psychosis?

A number of longitudinal studies have been conducted now across various stages of psychosis. These studies largely concur on the occurrence of progressive loss of brain tissue in psychosis at a rate greater than expected from healthy individuals.[19–21] However, these longitudinal changes are spatially constrained, temporally limited to the period following the first episode, and of modest magnitude.[22] Furthermore, subtle progressive gain also occurs alongside progressive loss, though this gain is not concentrated to selected regions; thus, tissue increases are not picked up at the sample level, but are notable in covariance analyses.[22–24] This phenomenon is clearly demonstrated in a recent cross-sectional study of individual deviations from normative models of cortical thickness and white matter integrity in schizophrenia.[25] Whereas 79% of patients show infra-normal deviations (i.e., < 5th percentile value of age- and sex-matched healthy individuals), 46% show supra-normal deviations (i.e., > 95th percentile value) for at least one brain region. Infra-normal deviations in thickness are more common in medial prefrontal, insula and lateral temporal regions (but in only 15%–20% of patients), whereas supra-normal changes are more common in occipital and paracentral regions (affecting 3% of patients), indicating distributed changes that lack regional specificity.[25] Furthermore, in a recent detailed appraisal of this issue of grey matter increase using a meta-analytical network mapping approach, Mancuso and colleagues[26] concluded that whenever grey matter reduction occurs in one brain region, concurrent grey matter increase occurs in other brain regions

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across various psychiatric disorders. Interestingly, such grey matter changes of opposite polarity occurred in distinct functional networks. In particular, these co-alterations often involved reduced grey matter in the task-negative default-mode network (which is often observed to be "deactivated" during externally focused tasks in functional MRI studies) while concurrent increase occurred in task-positive subcortical and cognitive control regions.[26] Taken together, these findings indicate that the phenomenon commonly considered to be neuroprogression may instead be a well-coordinated compensatory process operating across various psychiatric disorders.

Does neuroprogression indicate an unfavourable outcome?

The presence of lower grey matter volume at the outset of the first episode, even before treatment initiation, has been shown to be predictive of poor subsequent response.[27–29] Additionally, patients who have a longer duration of active symptoms show more longitudinal volume loss than those who are in remission.[30–32] Despite these reports, a causal relationship between postonset tissue loss and subsequent cognitive, functional or symptomatic decompensation is weakened by several observations. First, there is a notable lack of diagnostic specificity for progressive tissue loss. Relapses of various nature are associated with greater tissue loss, as reported in recurrent depressive disorder,[33] alcohol use disorder,[34] bipolar disorder,[35] migraine,[36] epilepsy[37] and chronic pain.[38] While there are likely differences in the affected brain regions among these illnesses, progressive tissue loss in these disorders is not suggestive of a decompensating trajectory. Second, the association between illness severity and grey matter loss is inconsistent. Several studies indicate a lack of association between tissue reduction and illness severity (as reviewed previously[22,39]). Some studies even indicate a reverse relationship, associating unfavourable outcomes to an increase in grey matter as opposed to a decrease.[40–42] Third, patients who are more symptomatic tend to receive higher doses of psychotropic medications, specifically antipsychotics, which hasten grey matter reduction.[43–45] Observational studies cannot resolve this confound. Hence, we cannot confidently conclude that neuroprogression is indicative of an unfavourable outcome in psychosis.

Does treatment delay worsen neuroprogression?

Many studies that report progressive tissue loss include participants who receive clinical care at specially constituted early intervention services, indicating that neuroprogression occurs despite early psychosocial and medical care.[46] While experimental reduction of the duration of untreated psychosis (DUP) improves functional outcomes,[47] observational studies relating duration of untreated illness to tissue loss are inconclusive.[19,21,43,48,49] A systematic review by Anderson and colleagues[50] examined 43 studies that investigated the association between duration of untreated psychosis and brain structure (imaged with a variety of modalities). Of these, only 8 studies showed statistically significant findings and, even among the brain regions identified as having significant structural associations, these findings were inconsistent across studies. Observational studies linking DUP to brain changes are limited because DUP is a complex variable affected by service availability as well as personal and family profiles. In addition, multiple measurement confounds have been neglected in prior studies. In particular, MRI studies have not separated cortical thickness, a malleable morphometric feature that is sensitive to plastic changes in adult life, from surface area or gyrification, which are largely determined during early brain development and show much smaller magnitude of changes in adult life.[51] A recent multimodal imaging study in medication-naïve first-episode psychosis reported that longer DUP relates to both reduced surface area and increased cortical thickness.[52] This contradicts the neuroprogressive hypothesis, which would predict larger reductions in brain features that are more malleable in adult life, such as cortical thickness, as opposed to features that are more developmentally determined. Rather than treatment delay causing structural changes, these findings are better explained by the fact that patients with developmentally determined structural deficits are more likely to receive delayed treatment, likely because of the insidious onset and the lack of a dramatic drop in functional levels given their premorbid deficits. This idea is supported by a large body of literature linking the indicators of developmental aberrations such as familial loading of illness risk,[53] poor premorbid adjustment,[54–56] early age of onset[56] and neurologic soft signs[57] with longer treatment delay. A prospective assessment of the same cohort, subjected to a 16-week trial of risperidone, revealed longer DUP to predict poorer treatment response.[52] While treatment delay diminishes the probability of favourable response, the relationship between these variables is unlikely to be mediated by progressive grey matter reduction. It is likely that the treatments we provide do not work well for latecomers,[17] who are likely to be those with developmental deficits.[58,59]

Neuroprogression: Illness or treatment effect?

A series of observational studies have implicated antipsychotics, especially in higher doses, in neuroprogression.[39,44,60] However, in clinical practice, patients who receive higher doses of antipsychotics are also often those with higher symptom burden and longer illness duration. Untangling the treatment from illness effects have been hitherto impossible, but 3 recent studies provide some clarity.

Liu and colleagues[61] recruited a rare sample of patients with nearly 20 years of untreated schizophrenia from rural Western China. When 2 matched groups of treated patients (risperidone or clozapine) with a similar duration of illness were compared, pronounced grey matter reduction was seen in the cohort treated with antipsychotics compared with the treatment-naive cohort. The treatment-naive sample did exhibit widespread grey matter reduction, but also grey matter increases in specific brain regions compared with age-matched healthy controls. Being a case–control study, the temporal association between treatment administration and tissue loss cannot be inferred.

In the Staged Treatment and Acceptability Guidelines in Early Psychosis Study (STAGES), Chopra and colleagues[62] randomized 62 patients to antipsychotic treatment or placebo, while providing psychosocial interventions to both arms. Three months after treatment, the medicated group had an increase in pallidal volume (likely related to D2-blockade effect), but the placebo group had a reduction in pallidal volume with a small effect size difference between the 2 arms. Interestingly, at 12 months, there were no differences between the 2 groups. Given the ethical constraints of a placebo-controlled study, this sample included only patients with short DUP (< 6 mo), only a low dose of antipsychotic was used, and patients showing poor response were removed from the triple-blind experiment, thus affecting generalizability.

In the Study of the Pharmacotherapy of Psychotic Depression II (STOP-PD II), Voineskos and colleagues[63] randomized 88 patients with psychotic depression who achieved 8-week remission from psychosis on sertraline and olanzapine, to either discontinue olanzapine (placebo arm) or continue for 36 weeks. The olanzapine group experienced a significant reduction in cortical thickness, but not surface area. In the placebo arm, relapses were also associated with thickness reduction, albeit with smaller effect sizes than olanzapine exposure. Interestingly, in the olanzapine arm, reduction in thickness was more likely in those who sustained remission than in those who relapsed. In the olanzapine arm, reductions were predominantly in the lateral frontotemporal cortex (pars opercularis and middle temporal region), but regional differences in relapse- compared with remission-related thickness reduction were not examined. Patients in this study had psychotic depression and an average age of 55 years. The generalizability of this observation to patients with other forms of psychosis, who tend to be much younger at presentation, is unclear.

From these reports, we can conclude that a notable portion of MRI-based grey matter reduction is antipsychotic related, while illness-related reduction also occurs and relates to the periods of active symptoms (relapses). Taken together, these observations challenge the neuroprogressive interpretation. Grey matter reduction occurs in the placebo arm in both randomized controlled trials (RCTs; though only for the first 3 mo in the data reported by Chopra and colleagues[62]), consistent with neuroprogression. But grey matter reduction is also associated with the administration of demonstrably efficacious treatment in both RCTs as well as in the chronic untreated sample reported by Liu and colleagues[61]; this would not be expected if it is the result of a progressive pathophysiology. Given the larger effect size seen in the treatment arm of STOP-PD II, one may posit that treatment itself somehow hastens neuroprogression despite demonstrating superior outcomes. However, this conclusion is contradicted by the fact that in the olanzapine arm, reduction in thickness was more likely in those who experienced sustained remission than in those who relapsed. This is the reverse of what was seen in the placebo arm, where thickness reduction was shown to be more likely in patients who relapsed. Furthermore, in the STAGES study, 12 months after treatment initiation, there were no notable differences between illness-related and treatment-related changes. While it is possible that the illness and its treatment affect the structure of different brain regions, all reductions in cortical thickness, irrespective of their regional localization, are considered deleterious under the premise of neuroprogression. If we accept the neuroprogressive interpretation, we cannot reconcile the contradiction that treatment-related structural changes appear protective, while the illness-related changes appear to be deleterious (as observed in STOP-PD II), with both processes resulting in similar brain anatomy over a longer period of time (as observed in STAGES).

How can we then explain the observation that both the illness and its treatment produce a similar change in the presumed pathophysiology? We propose that the observed progressive structural changes are reflective of physiologic adaptation rather than primary pathophysiology, and these compensatory efforts are facilitated, not alleviated, by treatment.

Neuroprogression as an adaptive change

When we start considering neuroprogression as an adaptive change, a number of paradoxical observations in the field start to fall in place. First, when considering long-term trajectories, progressive tissue loss does not reflect longitudinal worsening; in fact, patients treated with antipsychotics get better despite tissue loss.[64,65] Clozapine, arguably the most effective intervention for schizophrenia, increases the progressive tissue loss despite clinical and functional improvement.[66–68] Second, progressive tissue loss is not specific to psychosis or to any psychiatric syndrome or individual symptom. A large amount of the variance in structural changes is explained by a single p factor that captures the overall burden of psychopathology.[69] Many brain regions are altered by the majority of brain diseases, albeit to a variable extent.[70,71] Third, most patients with psychosis display a pattern of cortical thickness that is indistinguishable from that of healthy controls,[25,72,73] indicating that neuroprogression is an unlikely mechanistic process operating in a large majority of functionally disabled patients who need active interventions. If this is the case, reversing or arresting these brain changes may not bring the desired effects of early intervention.

The extant literature reviewed here indicates that putative neuroprogression is unlikely the primary pathophysiological process to be targeted for secondary prevention efforts in psychiatry. If we refrain from invoking the framework of a progressive pathophysiology, then the mechanistic basis for the onset (i.e., first episode) and later recurrences could be considered separable. In other words, the inefficient adaptive pathobiological processes that lead to recurrences (relapses or comorbidity) are likely distinguishable from the mechanisms triggering the onset.

Neuroadaptation as the mechanistic focus of early intervention

In many physiologic conditions, grey matter reduction confers an adaptive advantage (e.g., developmental cortical thinning[74,75] or pregnancy[76]). A higher rate of change of cortical thickness is associated with greater intelligence in healthy adolescents,[77] while pregnancy-associated grey matter reduction is

associated with improved maternal bonding.[76] While such an assertion in pathological states may be iconoclastic, it is important to recognize both benefits and costs of grey matter changes in psychiatric disorders before intervening to "protect" against them. Preclinical studies indicate that morphological changes induced by developmental adversity may indeed prime the organism for a more strategic response in the face of further adversity.[78] In this context, the term "neuroprogression" for post-onset structural changes in psychiatric disorders stands out as an unfortunate misnomer. A more accurate description of these MRI-based grey matter changes would be "cortical reorganization" or "structural neuroadaptation."[79]

Physiologic adaptation to perturbation is a feature of all complex biological systems, including the human brain.[80] While restoration of pre-perturbation parameters (healthy baseline) in patients is naturally the most desirable state, a chaotic response resulting in alternate states of stability is more likely with intense, protracted perturbations[81,82] (as in a psychotic episode). Such "exploratory" neuroadaptation may result in distributed, albeit small effect size changes in the brain structure and may continue until a new "steady state" is reached, which may be less than optimal[82] (inefficient compensation or maladaptive steady state[83]). In the context of systems biology, psychiatric phenomena can be seen as emergent properties;[84,85] their appearance as well as resolution cannot be fully solved by focusing on the properties of single constituent markers, such as MRI-based brain structural changes. A deeper understanding of this exploratory adaptive response is a requisite step for devising empirically informed secondary prevention strategies. In this case, intervention to modify illness trajectories would be different from the initial treatment and would focus on guiding more adaptive biological processes to emerge in an individual.

Investigating neuroadaptation in psychosis

The conventional approach in the field tends to view structural changes as a pathological outcome to be targeted for intervention (i.e., neuroprogression). In contrast, the systems perspective[82] acknowledges the inherently dynamic nature of brain structure, its interconnectedness with illness-related factors at various levels and the variations that may result from internal regulation to reduce the impact of external perturbations.[86] In this view, MRI-based structural changes are likely nested within a system of physiologic changes occurring at the molecular, cellular, tissue or organ (i.e., whole brain) level as well as the bodily changes that occur elsewhere in the course of psychosis (e.g., cardiometabolic changes). In addition to this interconnected system of biological changes, causal interactions also occur outside the body, at the level of individual and collective behaviour,[87] affecting the brain structure. As with other systems concepts, investigations of neuroadaptation require multi-scale and multi-level measures that employ network theory. At the level of brain structure, investigations that parse the relationship between various spatial units and tissue types are needed (e.g., graphs of concomitant grey matter and white matter changes, relationship between grey matter reduction across different brain areas). These structural graphs depicting an observed state of interaction must then be studied in conjunction with graphs capturing the emergent properties of interacting signals of brain function (e.g., co-occurring changes in functional activity and symptom-based, cognitive and behavioural networks[88]). Crucially, as neuroadaptation results from autoregulatory, self-organizing processes, they are likely not defined by discrete, observable events but occur gradually over time. Characterizing dynamic neuroadaptation processes will require multi-level, multimodal measurements to be repeatedly captured over time.

An implicit speculation that arises from the proposal here is that antipsychotics may assist the process of neuroadaptation. The evidence to date, in our view, supports the notion that post-onset thickness change (reduction and increase) may indeed be an adaptive process. There is also emerging evidence that antipsychotics contribute to thickness reduction. Nevertheless, there is no evidence to assume that the antipsychotic-induced thickness reduction per se is therapeutically beneficial. In due course, the antipsychotic- versus illness-related thickness changes may turn out to be distinct in their spatial distribution across the brain, the underlying histological changes (e.g., increased intracortical myelination v. grey matter atrophy), the cellular constituents affected (e.g., glial v. neuronal changes), the time course (continuous or time-limited effects) as well as the potential reversibility. None of this information is presently known. Experimental "on–off" studies of antipsychotics in selected patients with multiple within-subject observations and careful characterization of symptom and functional changes are required to parse these phenomena further. Noninvasive experiments that induce short-term adaptive changes (e.g., sensory- or motor-deprivation paradigms[89]) may be feasible in both medicated and unmedicated patients. Such experiments will provide clarity on whether antipsychotics assist or interfere with presumed adaptive processes. Until such evidence is available, antipsychotic-induced structural changes should be considered with caution.

There is a clear need for energetically promoting early intervention in psychiatry. The psychosocial toxicity of untreated psychiatric illness is irrefutable; this forms the sufficient premise to vigorously promote early intervention. Treatment delay in psychiatric disorders occurs due to systemic factors such as chronic underinvestment in effective service delivery, societal factors pertaining to stigma, and personal health belief models. Addressing these issues remains the primary and urgent goal of secondary prevention in psychiatry. Early intervention provides substantial benefits at a program level,[50] but our arsenal for providing effective, minimally invasive and acceptable early intervention for the patients with varying illness severity that we see at our clinics remains inadequate. Linking early intervention to deleterious neuroprogression is untenable at best, and may hamper the progress of further enquiry into mechanistically informed secondary prevention in psychiatry. It is time for the neuroscience of early intervention to take a decisive turn away from the dark alley of neuroprogression.

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